Endocrine Disruptors Research Program
Summary of BOSC Comments, 2005 Proposed ORD Actions
And Progress in 2007

Recommendations	2005 Proposed Action Items	Progress
1). Progress reviews are encumbered, to some extent, by the difficulty in defining the scope of activities considered "endocrine disruptor research." There are a large number of toxic mechanisms that could be categorized as endocrine disruptors: therefore, EPA should clarify what is and is not covered by the EDC program whenever the program is reviewed (p. 7, 30, 41).	Action: ORD's Research Plan for Endocrine Disruptors and the MYP for Endocrine Disruptors reference the definition that is used to guide this Research Program. The guiding definition, what research is included, and how this relates with other ORD research will be further clarified in the next update of the MYP and in future Program Reviews Time Line: The Endocrine Disruptors research planning team is updating the MYP. A draft of the update will be available in early 2006. A mid-course review of the Research Program will take place in late 2006.	The updated draft MYP has adopted the definition of endocrine disruptors that the WHO published in 2002. Furthermore, the draft MYP clarifies that the emphasis of EPA's research program is on impacts on the estrogen, androgen, and thyroid systems. It also points out that there are additional research efforts ongoing, to a smaller extent, on other mechanisms, including through steroidogenesis, aromatase, and the hypothalamic-pituitary-gonadal and hypothalamic-pituitary-thyroid axes.
2). The following are recommendations that would allow the Program Director to negotiate for needed research expertise from a position of strength and enhance the laboratories that participate in EDC program research: (1) hire additional personnel to share the workload of the participating laboratories; (2) elevate the position of the EDC Program Director to the level of the Laboratory/Center Directors; and (3)	Action: (1) The EDCs Research Program will be bringing on board several new postdoctoral fellows to fill critical gaps and help advance the Research Program. The NPD will encourage the Laboratories/Centers to pursue other Fellows (e.g., AAAS, ASPH) and will work with ORD's Office of Resources and Management Administration to explore the possibility of using other vehicles (e.g., recent graduate contract) to supplement the number of scientists in this Research	(1) A few new hires were made and EPA workforce was supplemented/complemented with postdoctoral fellows, ASPH fellows, graduate students, 'recent student' contractors. There has been better leveraging of personnel across research programs, sometimes by realigning them. (2) and (3) Working out the relationship of the NPDs and other ORD senior managers has been an ongoing effort; there is a draft document "*Roles and Responsibilities of ORD's Senior Research Managers"* (August 2007) that is currently undergoing review. The ORD SBO is on record as having budget authority for the organization.

provide the EDC Program Director budget authority. (p. 7-8, 14).	Program. (2) The NPDs report individually to the Assistant Administrator (as do the Laboratory/Center/Office Directors) through the Deputy Assistant Administrators and work together as a group to assist in planning and implementing ORD's Research Programs. They are awarded senior level stature and make recommendations to the Laboratory/Center Directors, the Assistant Administrator, and Deputy Assistant Administrators (i.e., collectively the Executive Council) regarding research priorities. The details regarding the relationship of the NPDs, to the Executive Council, Science Council, and other Agency groups are being delineated in a document under development. (3) "Budget authority" resides with the SBO in ORD. The Executive Council decided that budget advice and recommendations will be sought from the NPDs who would be responsible for working closely with the Laboratory/Center/Office Directors Time Line: (1) Finding innovative ways to supplement the existing EDCs workforce is an ongoing effort. Furthermore, as the NPDs begin to work together, they may be in a better position to characterize leveraging of personnel across the Research Programs. (2) and (3) Details of the relationship of the NPDs within the ORD management structure are being worked out in a document under development by ORD and will be available by January 2006.	
3). To meet the program goals and	Action: As noted in the BOSC review, ORD has complemented its strengths in the	Some of the new postdoctoral fellows have training in the area of wildlife toxicology. There has been improved leveraging: across ORD research

fulfill the exact needs of regulatory concern the BOSC recommends that the EDC program dedicate full-time EPA personnel to work in this [wildlife toxicity] area (p. 9, 22).	areas of aquatic and human health related toxicity by engaging academic wildlife toxicologists through the extramural STAR program and will continue to do so, where appropriate. It is anticipated that some of the new post doctoral fellows that will be sought will be in the area of aquatic or invertebrate toxicology which will strengthen our ecological portfolio but will not move into other wildlife research. We will increase our efforts to collaborate across federal agencies to leverage the talent of their wildlife toxicologists. The EDCs Research Program is working with a contractor to have a synthesis document developed that is integrating the published results from ORD's extramural STAR and intramural programs on the impacts of EDCs on wildlife, including aquatic, amphibian, invertebrate, avian, reptile species. Time Line: The NPD will work through the Interagency Working Group (IWG) on Endocrine Disruptors to increase sharing of information and leveraging research activities. One collaboration already underway is the organization of a multi-Agency sponsored workshop to look at the impact of wastewater treatment plants and concentrated animal feeding operations (CAFOs) on ecosystems. It will be held in 2006. The synthesis report on wildlife will be completed late in 2005.	programs and across federal agencies. There was an interagency working group workshop on impacts of EDCs on ecosystems and the environment in February 2007 where research activities were shared and areas for increased collaborations were identified. Another workshop on CAFOs was held in August 2007 that brought together scientists from other Agencies, from ORD, and OW to meet with the newly awarded grantees and develop collaborations. ORD scientists collaborated with a team of Canadian scientists to evaluate the long term impacts of dosing an experimental lake with low levels of estrogen. A draft report that synthesizes the results from the intramural and extramural research programs includes a chapter on wildlife (2007) has been developed.
4). Because of the complexities in extrapolating among the many species in the environment that may be affected by endocrine disruptors, it	Action: Our intramural Research Program will continue to evaluate potential interspecies differences and similarities among the various cellular mechanisms of	Research on cross species extrapolation is an integral part of many of ORD's research programs. Under the EDCs program intramural research will be continuing through FY13. There are other complementary efforts are ongoing through the SP2 and Comp Tox research programs. For example,

will be important for ORD to continue to collaborate with other federal, academic, nongovernmental (NGO), and industry partners to characterize better the range of variability among species (p. 9, 22).	action of current interest in the EDCs Research Program. Currently, these efforts include identifying the androgen receptor and estrogen receptor of different species, examining the response of these receptors to the same compounds using *in vitro* methods, as well as conducting a comparison of the *in vivo* response in several species. This work is being conducted in conjunction with investigators at two universities and a chemical company in Germany. In addition, our scientists will continue to collaborate with scientists from other organizations. This will be done on a scientist-to-scientist basis as well as under the auspices of the IWG. Time Line: Our Research Program on species extrapolation is scheduled to continue through FY07. The topic of extrapolation across species will be raised at a meeting of the IWG in the fall of 2005 to determine whether there is any interest in having a future workshop on this topic.	the Comp Tox program is assisting in the development of databases for PBPK models and data from their ToxCast initiative as well as from the Agency's Endocrine Disruptors Screening Program will enable us to better understand species similarities/differences.

5). Studies have been reported regarding the use of predictive tools that can be used to prioritize the focus of specific treatment technologies and compounds. These findings could be integrated into EPA's EDC program (p. 9, 22).	Action: The NPD and the EDCs and SP2 planning teams will work with the Director of the National Center for Computational Toxicology (NCCT) to ensure greater linkages among the EDCs, Comp Tox, and SP2 Research Programs. These will be better characterized in the updated MYPs. Time Line: Comp Tox research is making progress in developing predictive tools for EDCs. The directions of the Comp Tox	There is research ongoing in EDCs, SP2, and Comp Tox (e.g., STAR and ToxCast) programs to develop predictive tools for determining the potential toxicity of chemicals. The EDCs MYP draft more clearly identifies the linkages with the other programs. The Comp Tox and SP2 programs have had their own BOSC reviews where these complementary efforts have been evaluated. Periodically held workshops have brought intramural and extramural scientists together to share approaches and findings. In 2007 a Comp Tox RFA through the STAR extramural program was issued for 2 new centers on development of predictive environmental and biomedical computer-based simulations and models. In the early years of the EDCs research program there was a modest effort on the development of predictive

	Program underwent a review by a Subcommittee of the BOSC in April 2005. A workshop that brought together STAR grantees and EPA scientists was held on July 17-18 to share their research and build collaborations. A draft of the EDCs MYP will be ready by early 2006 and will include clearer linkages among the EDCs, Comp Tox, and SP2 programs.	tools for risk management approaches. However, because of severe reductions in resources, those efforts have been discontinued.
6). The model and framework for development of critical information on EDCs for risk assessment is well established and progress is being made. Efforts now should focus on the development of risk assessment paradigms for EDCs and application of the research findings (p.21).	Action: EPA will continue to monitor research results that may affect current risk assessment practices, as they get published. If, and when, the Agency determines that risk assessment approaches need modification, they would convene a cross-Agency committee (as has been done with the development of other risk assessment guidelines) to deliberate and develop guidelines. In keeping with the guideline development process, there will be opportunity for public involvement, through workshops and solicitation of public comments. Time Line: Research that may affect current risk assessment practices will be monitored on an ongoing basis.	ORD research is studying the impact of cumulative risk for groups of chemicals with similar modes of action. In particular the EDCs research has focused on disruptors of the thyroid and androgen systems. A number of IRIS assessments are underway for chemicals with similar modes of action. ORD has developed a case study for incorporation of toxicogenomics data into a risk assessment of an endocrine disruptor. In the meantime, EPA's position remains the same - that current approaches for risk assessment under specific endpoints are appropriate for use in evaluating EDCs. Research by other scientists is routinely monitored. A workshop that would convene EPA and other scientists to determine the state of the science and to identify key research needs in the area of cumulative risk assessment is in its early stages of organization.
7). EPA should continue to improve its interactions with other agencies that have a strong interest in EDCs to identify new sources of environmental and human exposures, including investigating the role of pharmaceuticals as sources of EDCs. EPA should mine data made available from the HPV Program (p. 11, 30).	Action: The NPD chairs the IWG on Endocrine Disruptors and will use this opportunity to strengthen our relationships with the other Agencies. Efforts are already underway to organize a multi-Agency sponsored workshop related to sources of exposure. The IWG decided to focus this workshop on looking at the impact of two exposures, wastewater treatment plants and concentrated animal feeding operations (CAFOs), on	Through an interagency working group on endocrine disruptors a workshop on the impacts of EDCs on ecosystems and the environment was held in February 2007 to identify further collaborations. A separate IWG on pharmaceuticals in the environment is developing a research framework (December 2007). The updated EDCs MYP includes a small amount of research on endocrine active pharmaceuticals and will leverage activities with other ORD research programs that will address other classes of pharmaceuticals. A CAFOs workshop was held August 2007 that brought together scientists from EPA, other federal agencies, and our newly awarded grantees to share approaches and build collaborations. The Comp Tox program is leading coordinated international efforts with OPPT and the

	ecosystems. The NPD will continue to work closely with the co-chairs of the interagency PPCP task group and look for opportunities for joint efforts. The NPD will work with the NPD for WQRP to explore leveraging PPCP activities. In updating the EDCs MYP, the planning team will consider linkages with the WQRP's PPCP efforts. The NPD will work with OPPTS to make the data not only from HPV but also from VCCEP, available to ORD for data mining and research hypothesis generation. Time Line: The interagency workshop on wastewater treatment plants and CAFOs will be held in 2006. A STAR grantee and EPA scientist-to-scientist meeting on pharmaceuticals in the environment was held August 23-25. Some of the ORD EDCs research was presented at the workshop. The proceedings of this workshop are being distributed. The interagency Task Force also held a workshop on July 25-26 that was attended by some of ORD's EDCs researchers. The products of the workshop will contribute to the development of the Framework document, whose first draft is anticipated by December 2005. The SETAC workgroup will convene at the annual meeting in Baltimore in November 2005 to discuss organization and workgroup activities, including establishing potential subgroups on environmental effects, environmental risk assessment, fate and PEC, water treatment and management, future criteria for risk management, and mixtures. The NPD will be meeting with	OECD on molecular screening initiatives and developing 'one-stop' tox data bases. For example, the Comp Tox program is in discussions with OPPT to incorporate tox data from HPV information system into an aggregated computational toxicology system

	the OPPTS Office Directors in September about ways in which to improve communications of research results and will use that opportunity to request access to HPV and other data for the EDCs scientists. The NPD and MYP team will consider opportunities for incorporating the HPV and VCCEP data base mining activities in the next update of the MYP scheduled for completion in early 2006.	
8). It was not feasible for scientists conducting epidemiologic studies to attend the face-to-face program review meeting. Even though the subcommittee members were provided information from the Tulane conference and one of the subcommittee members attended the conference, the BOSC recommends that subsequent reviews of this program include poster presentations by each of the scientists funded by this interagency program (p. 30).	Action: The grantees will be brought together next summer for another grantees progress review. In the future the NPD and the planning team will avoid scheduling progress reviews of grantees near the time of anticipated Program Reviews. For the next Program Review, an invitation to the epidemiology grantees will be extended requesting their participation. Time-line: The NPD and planning team and the IWG will continue to track the research of this group of epidemiologists. Another progress review is being planned for next summer. The grantees will be invited to participate in the 2008 EDCs Program Review.	In 2006, EPA sponsored an endocrine disruptors progress review workshop at which all 5 of the EPA-sponsored epidemiology grantees presented their progress. Due to the complexity of research projects of this type, variable success in recruitment, delays in urine and blood sample analysis (backlog at CDC), and several administrative delays, the grants have been extended with no additional funding. All of the grants have submitted up-to-date progress reports in the past year. Several of the projects have produced significant publications, as well as frequent presentations at scientific meetings and are expected to result in reliable data. Final reports on all epidemiology grants are expected in FY2009. An invitation will be extended to the investigators requesting their participation at the next BOSC review.
9). It will be important for EPA to take the leadership role in the application of the "omics" technologies to address many of the science questions critical for evaluating environmental and human health effects of EDCs. This will require a strong commitment to a systems biology approach and computational toxicology as well as	Action: EPA is positioning itself as a leader in the 'omics field through research and policy developments. EDCs scientists will continue to play a critical role in both of these areas. The Director of NCCT and the NPD will continue to hold frequent meetings to coordinate activities. They will work with the planning team to ensure that the linkages among the Comp Tox,	EDC scientists are playing a role in research and policy developments. Some of the scientists are participating in activities under the Agency's Genomics Task Force which has the lead for the Agency in coordinating genomics activities. ORD is developing a repository for array data and holding training workshops for EPA. High-density data approaches are being incorporated into ecologic and human health risk assessment based research for multiple research programs (e.g., EDCs, Human Health , Drinking Water, SP2). NCEA has developed a case study on incorporation of toxicogenomics data on an EDC into risk assessment.

effective interactions with those generating much of the basic data (p. 11, 30, 36)	EDCs, and SP2 programs are captured in the updated MYPs. Time Line: The update of the MYP will be available in early 2006. Interaction with the Office of the Science Advisor's Genomic Workgroups is expected to continue for the foreseeable future, as confirmed at the Genomics Training and Tools collaboration meeting with FDA/NIEHS/ICCVAM held on August 4, 2005. The use of toxicogenomics data in risk assessment case study will have a draft for internal review by June 2006. A Workshop review of the case study will be completed by September 2007.	

10). EPA should continue to investigate the common ground between ecological and human health because the Agency is in a unique position to do so (p.11, 30).	Action: The NPD and the planning team will take on the challenge to develop approaches that integrate human health and ecological assessments. We will consider improving the integration of projects that will contribute to evaluate human and ecological health (e.g., using the MOA approach). A pilot for this consideration may be centered around CAFOs, where we will be increasing our intramural efforts and issuing a STAR solicitation. Time Line: Discussions regarding the directions of the EDCs Research Program are ongoing. Within the next year, several post docs will be brought on board to expand our research efforts on CAFOs. In addition, an RFA is under development to issue this fall to engage the academic community to focus on CAFOs. The	There has been a moderate degree of activity to address this recommendation; The previously reported case study on MOA of BPA was published in 2005. The research on cross-species extrapolation looking at ER and AR and on aromatase in fish and rat will be valuable in exploring the bridge between ecological and human health. The five grants that are developing exposure methods for complex environmental or biological media will also provide a bridge since their results can be used for environmental or human monitoring studies. Potential interagency collaborations regarding conducting an integrated multidisciplinary study that encompassed ecological and human health were discussed at IWG workshop in 2007 but not pursued further. In our proposed actions we suggested that a pilot to look at the common ground between ecological and human health may be conducted in relation to the CAFOs research project. However, most of this effort is focusing on charactering the occurrence of endocrine activity, its impacts on ecological health, and the development of remediation approaches. It may be possible to add a component in the future, depending on resources, which could evaluate potential impacts on human health in communities where CAFOs flourish.

	update of the MYP will be available in early 2006. The MOA case study was finalized in June 2005.	
11). ORD is beginning to develop core competencies in genomics and quantitative structure activity relation (QSAR) methods, both of which hold promise in endocrine disruptor identification. Because these areas are so data intensive, it will be important for ORD to train or hire experts in bioinformatics to work with the life sciences experts already on staff (p. 8, 24, 36)	Action: ORD is addressing the need for increasing our competency in bioinformatics in two ways. The first is with new hires. The National Exposure Research Laboratory already has hired two bioinformaticians. The NCCT has issued job announcements for an additional two intramural bioinformaticians. Second, we have issued a solicitation through STAR for an Environmental Bioinformatics Research Center. The award for the EBRC will be made in the form of a cooperative agreement so that there will be strong interactions between extramural intramural scientists. Time Line: Two hires have been made. Two additional positions have been advertised and applications received. It is expected that selections for the latter two positions will be completed by October 15, 2005 with the persons joining the staff of NCCT soon thereafter. The awards for the EBRCs will be made by September 30.	Significant progress has been made in this area. NHEERL established a genomics core. NERL established a metabolomics core. Cooperative agreements have been established with 2 EBRCs for strong interactions with ORD scientists, in particular those from NCCT. As such, there are frequent communications and yearly workshops that bring the intramural and extramural scientists together. NCER issued a 2007 RFA for 2 new centers on the development of predictive environmental and biomedical computer-based simulations and models. NHEERL hired a toxicogenomic expert and systems biologist. NERL hired a bioinformatician. NCCT has hired three senior level scientists to work in the areas of bioinformatics and computational systems biology and has added 5 post docs working on various computational models
12). The transfer of protocols to contract laboratories has been problematic. This has led to a substantial commitment by EPA staff to refine and troubleshoot assays, and it has had a negative effect on other core research activities that are the responsibility of ORD staff. The BOSC recommends that there be a	Action: OPPTS senior management and the NPD will be meeting with NHEERL senior management to emphasize OPPTS' priorities and time lines and to reach agreement on how to meet their expectations. Time Line: Meetings are being set up in Research Triangle Park and Duluth in	Significant progress has been made in completing the research needed to develop and standardize assays for the Agency's EDSP. The Tier 1 assays are in various stages of validation by OPPTS for use in implementation of EDSP. All of the Tier 1 assays will be validated and peer reviewed by the time EDSP is implemented in 2008. OPPTS has published its plan for peer review. Remaining research is being conducted in finalizing the fish and the frog life cycle assays for implementation in Tier 2. These assays will be handed off to OPPTS for validation in 2010. ORD scientists, throughout this process, continue to serve as valuable resources to OPPTS as the assays are

mechanism in place to ensure the timely transfer of protocols to OPPTS (p. 35).	September.	validated, under peer review, and ultimately implemented. Research ongoing under Long Term Goal 1 will help provide OPPTS with the foundation it needs to interpret the data as they are submitted to the Agency. ORD scientists will serve as consultants at that time as well.

13). This research is diffuse and is occurring in multiple divisions within NHEERL and many of the accomplishments in these areas have been difficult to capture in the list of APGs. The BOSC recommends that EPA try to summarize this research and its relevance to EDC identification in subsequent reports and revisions of the MYP (p.35).	Action: The EDCs planning team is beginning to update the MYP. It will develop a more coherent way in which to summarize the accomplishments to date and characterize their impact and cite linkages to other relevant documents, such as the NHEERL Implementation Plan, the National Risk Management Research Laboratory's Risk Management Evaluation for Endocrine Disruptors, the Comp Tox Implementation Plan, and the MYPs of other Research Programs, e.g., SP2, Human Health, WQRP. The research is also being summarized in three topical synthesis documents (Effects in Wildlife, Effects on Development, Screening & Testing) that will compile and integrate the intramural and STAR extramural research accomplishments. Time-line: The NHEERL Implementation Plan on Endocrine Disruptors was updated in October 2004 and included in the background materials for the Program Review. The synthesis documents will be available late in 2005. A draft of the updated EDCs MYP will be available early in 2006.	It remains a challenge to portray the significant accomplishments in a coherent way in the updated MYP draft. Multiple approaches are being used. A draft synthesis document has been prepared through the use of a contractor that summarizes and integrates intramural and extramural accomplishments. The research is organized under three main topics – Wildlife, Development, and Screening and Testing. In the draft MYP accomplishments have been aligned under annual performance goals in an Appendix. This is still in a preliminary stage of development. Research products are also captured in a bibliography that has been compiled of over 500 peer reviewed publications. The bibliography has undergone a bibliometric analysis. A website for broad communication of results is under development.